Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-126, 129-131 are pending in this application and are rejected on various grounds. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 USC § 101 and 112, First paragraph

Claims 119-126 and 129-131 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 119-126, 129-131 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention."

The Examiner states that "the asserted utilities of cancer diagnostics and cancer therapeutics for the claimed antibodies are credible and specific. However, they are not substantial". The Examiner notes that "literature reports that gene amplification does not necessarily result in increased expression at the mRNA and polypeptide levels" and quotes exemplary references like Pennica *et al.*, Konopka *et al.* and Haynes for support. For the reasons outlined below, Applicants respectfully disagree.

Utility Standard

In interpreting the utility requirement, in *Brenner v. Manson* [1] the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form." [2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but

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[1] *Brenner v. Manson* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy." [3]

Later, in *Nelson v. Bowler* [4] the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility." [5]

In *Cross v. Iizuka* [6] the CAFC reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between." [7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility." [8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face. [9] The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the

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[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F. 2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid*

utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." [11], [12]

Compliance with 35 U.S.C. §101 is a question of fact. [13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. [14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines") [15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on

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[11] *In re* Langer, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (CCPA 1974).

[12] See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re* Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Proper Application of the Legal Standard

Applicants maintain that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the instantly claimed 'native sequences' of the PRO1112 polypeptide of SEQ ID NO: 207 for the reasons outlined below. Applicants also maintain that a *prima facie* case has not been made for lack of utility by the Examiner and that the present disclosure is sufficient to establish a specific, substantial and credible utility for the PRO1112 polypeptide. Applicants address each rejection made by the Examiner below. In particular, it is maintained that the gene amplification assay clearly shows that the nucleic acid encoding PRO1112 is significantly overexpressed in human tumor tissues as compared to a non-cancerous human tissue control and that this data is sufficient and is not preliminary. For example, Table 8 explicitly states that the nucleic acid encoding PRO1112 is significantly overexpressed in lung adenocarcinoma tumors and some colon tumors as compared to the normal control. The specification further teaches that the PRO1112 polypeptide and its native sequences with 80-99% identity are also useful as diagnostic markers for detecting the presence of one or more lung adenocarcinomas and certain colon tumors. This utility is in currently available form and is substantial based on the gene amplification data.

Regarding Pennica *et al.*, Konopka and Haynes, Applicants respectfully maintain that, for the reasons previously set forth in the Applicants' response filed July 16, 2004, Pennica *et al.*,

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[16] M.P.E.P. §2107.01

[17] M.P.E.P. §2107 II (B) (1)

Konopka and Haynes do not show that a lack of correlation exists between gene (DNA) amplification and elevated mRNA levels, in general. Therefore, the Examiner cannot make a *prima facie* case for lack of utility based on these references, as discussed further below. The Examiner says on Page 4 of the Office action that "Applicants argues that the WISP-2 or abl genes may be discrepancies". Applicants respectfully disagree. Instead Applicants maintain that, as discussed in their previous response, Pennica's teachings discuss WISP genes only and not genes in general, and therefore, Pennica's teachings do not meet the *'more likely than not* standard' and do not support the showing that gene amplification is not associated with increased mRNA or increased protein levels, in general. Similarly, Applicants discussed that Konopka only address the *abl* gene, again not genes in general, and is therefore not an appropriate reference for making a *prima facie* case for lack of utility.

In fact, the Haynes reference, contrary to the Examiner's reading, teaches that "there was a *general trend but no strong correlation* between protein [expression] and transcript levels" (Emphasis added) even though protein levels could not be accurately predicted. For example, in Figure 1, there is a positive correlation between mRNA and protein levels amongst most of the 80 yeast proteins studied. In fact, very few data points deviated or scattered away from the expected normal and no data points showed a negative correlation between mRNA and protein levels (i.e. an increase in mRNA resulted in a decrease in protein levels). As discussed above, the law does not require the existence of a "strong" or "linear" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately" predicted. According to the authors themselves, the Haynes data confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in Haynes *et al*, and application of an improper, heightened legal standard.

On page 6 of the Office action, the Examiner says that "it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels." Applicants respectfully submit that in Table 9A, PRO1112 was showed Ct increases in lung tumor samples LT10 (1.135), LT11 (1.525), LT12 (1.195), LT13 (1.635), LT15 (1.775), LT17 (1.455), LT18 (1.255) and colon

tumor CT2 (2.265). These increases would not be considered small by one skilled in the art and instead are significant and correlate well with diagnosis of cancer and provides "specific benefit in currently available form."

The Examiner further asserts that "(f)urther research is needed by the skilled artisan to determine if the disclosed results regarding a gene amplification event in tumors is also reflected at the mRNA and polypeptide levels." Applicants respectfully disagree.

As stated above, in explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions that **Office personnel must be careful not to interpret the phrase "immediate benefit to the public"** or similar formulations used in certain court decisions **to mean that products or services based on the claimed invention must be "currently available" to the public** in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a '"substantial" utility'"[18] (emphasis added). Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement states, "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." Accordingly, Applicants respectfully submit that Applicants' assertion that the claimed PRO1112 proteins have utility in the field of cancer diagnostics is substantial. Further, Applicants had previously presented three articles by Orntoft, Hyman and Pollack *et al.* and their data clearly showed that, in a large number of genes amplified in tumor cells, there was increased gene expression. Since this showing was in a large number of genes, the teachings meet the "*more likely than not*" standard.

Regarding the Orntoft *et al.*, Hyman and Pollack *et al.* references, the Examiner says that they "do not appear to look at gene amplification mRNA and polypeptide levels from a single gene at a time," and that they "concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes." The Examiner adds that such analysis was not done for the instant PRO1112 molecule. The Examiner also adds that "(t)he three papers

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[18] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form". Applicants respectfully disagree.

Applicants submit that, in Ornoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Ornoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Ornoft *et al* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Ornoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Ornoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Ornoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Ornoft *et al.* clearly support Applicants position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

The Examiner indicates that Applicants have not indicated whether PRO1112 is in a gene cluster region of a chromosome. But Ornoft *et al.* did not limit their findings to only those regions of amplified gene clusters and further, as discussed below, Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

The Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs were hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines were hybridized on the same

microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

The Office Action also states that the Dr. Polakis Declaration is insufficient to overcome the rejection "since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels and not gene amplification levels and protein levels". Applicants agree but indeed, if the Polakis Declaration were not relevant, then neither should the Hu *et al.* reference cited by the Examiner, since Hu also concerns the correlation between mRNA and protein levels (see discussions below).

Further, the Office action alleges that only Dr. Polakis' conclusions are provided in the Declaration. There was allegedly no evidentiary support to Dr. Polakis' statement that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide".

Applicants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew. [19] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument" [20] Furthermore, the Federal Court of Appeals held in *In re Alton*, "[w]e are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner" [21]. Applicants

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[19] *In re Rinehart 531* F.2d 1084, 189 USPQ 143 (CCPA 1976) and *In re Piasecki* 745 F 2d. 1015, 226 USPQ 881 (Fed. Cir. 1985)

[20] *In re Alton* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker* 977 F 2d at 1445, u2 USPQ2d at 1444.

[21] *In re Alton*, supra

also respectfully draw the Examiner's attention to the Utility Examination Guidelines[22] which states that, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered". The statement in question from an expert in the field (the Polakis declaration) states: "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis declaration, this rejection is improper under both the case law and the Utility guidelines.

According to the Examiner, Hu et al. shows that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. Hu teaches that among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. Applicants further respectfully submit that the Hu et al. reference does not show a lack of correlation between gene amplification data and the biological significance of cancer genes, for the reasons outlined below.

As a preliminary matter, it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not, as the Examiner suggests, whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

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[22] Part IIB, 66 Fed. Reg. 1098 (2001)

First, the analysis by Hu et al. has certain statistical flaws. According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Secondly, Applicants submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules are overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusions based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and **cannot be generalized as a principle governing microarray study of breast cancer in general**, let alone the various other types of cancer genes in general. In fact, even Hu *et al* admit that ., "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-

positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "[t]his may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). Therefore, the Hu reference is not appropriate since again, it too does not teach that it is more likely than not, for genes in general, that DNA amplification does not result in increased protein levels.

The Office Action also says that the Ashkenazi declaration is insufficient to overcome the instant rejection because further research is required.

Again, as discussed above in the Utility guidelines and the arguments provided therein, "Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. " In Dr. Ashkenazi's opinion, even if the protein were no over-expressed, the simultaneous testing of gene amplification and gene product over-expression would enable more accurate tumor classification. To support this reasoning of Dr. Ashkenazi, Applicants had submitted the article by Hanna and Mornin, to demonstrate that, as in the example of the HER-2 gene, testing both gene and gene product (protein) lead to a more accurate classification of the cancer and more effective tumor treatment.

Applicants submit that, based on the results presented in the gene amplification assay for PRO1112 DNA, one skilled in the art would know that the corresponding polypeptide and antibodies have credible, specific and substantial asserted utility, for example, in detecting over-expression or absence of expression of PRO1112. This conclusion would be based on the art which indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. None of the references provided by the Examiner compellingly met the standard for most genes or gene classes in general. Instead, the references either referred to a single, few or a singular class of gene(s) with a lack of correlation between DNA and protein levels. In fact, some of the references referred to statistical analysis of data, where data had to be selected to provide meaningful interpretations. In the process, representation of "most genes" was lost and thus, conclusions can only be applicable to a

particular class of genes studied (for example, breast cancer genes in Hu et al.). Correspondingly, Applicants provided evidence to meet the "more likely than not standard" and Declarations by experts based on their personal experience and/or literature articles as to why utility is credible. The additional experiments, if any, are routine in the art, based on the teachings in the specification and the knowledge of the skilled artisan, at the time the application was filed.

Thus, Applicants maintain that they have demonstrated utility for the PRO1112 polypeptide and antibodies thereof as diagnostic markers for detecting adenocarcinomas or squamous cell carcinomas of human lung. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

Hence, these data clearly support a role for PRO1112 as a lung or colon tumor marker. Thus, Applicants request that the present 35 U.S.C. §101 and §112, first paragraph rejections to the pending claims be withdrawn.

Claim Rejections – 35 USC § 112, first paragraph- Written description

Claims 119-123, 130 and 131 remain rejected under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. The Examiner contends that "(i)n the instant case, only one polypeptide sequence has been identified with a potential link to cancer as recited in the claims. No other species have been disclosed. One species is not adequately representative of the many sequences encompassed by the claims". Applicants respectfully traverse this rejection.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[23, 24] The adequacy of written description support is a

[23] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

factual issue and is to be determined on a case-by-case basis.[25] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.[26, 27]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[28] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field."[29] Further, the hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity, have the capability of understanding the scientific and engineering principles applicable to the pertinent art" (Emphasis added).[30, 31]

The Disclosure Provides Sufficient Written Description for the Claimed Invention

Applicants submit that the instant specification evidences the actual reduction to practice of a full-length PRO1112 polypeptide of SEQ ID NO: 207, with or without its signal sequence. Thus, the genus of **native polypeptide sequences** with at least 80-99% sequence identity to SEQ ID NO: 207, and which possess the functional property "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors" would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

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[24] *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

[25] *See, e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[26] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[27] *See also* MPEP §2163 II(A).

[28] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[29] *See also* MPEP §2141.03.

[30] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988).

[31] *See also* MPEP §2141.03.

Applicants point out that the Specification describes methods for the determination of percent identity between two amino acid sequence. The Specification further describes methods for one of ordinary skill in the art to *identify* peptide sequences having at least 80-99% identity to SEQ ID NO: 207 'wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors' by testing the nucleic acids encoding these variants in the gene amplification assay which is well-described in Example 90 of the instant specification. One of skill in the art could readily test these variant native polypeptide sequences to determine whether its encoding nucleic acid is amplified in lung or colon tumors based on the step-by-step methods set forth throughout the specification and in Example 90. Accordingly, the specification provides adequate written description for native polypeptide sequences having at least 80% identity to SEQ ID NO: 207 wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors. For the above reasons, Applicants respectfully request that the rejection be withdrawn and the claims be allowed.

The Examiner is therefore respectfully requested to reconsider and withdraw the present rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C13).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: June 3, 2005

Daphne Reddy
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